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Multicenter Study on Hepatitis C Virus Infection in Patients With Dilated Cardiomyopathy

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Preliminary epidemiological and histological studies from Japan suggested that hepatitis C virus (HCV) infection has a role in the development of dilated cardiomyopathy (DCM). This multicenter study was conducted to verify this hypothesis on a large cohort of Italian patients with end-stage heart failure. Antibodies to HCV were determined in the 752 consecutive patients (608 males and 144 females; age, 53 ± 13 years) who entered the waiting list for cardiac transplantation from 1995 to 1997 at the six cardiac surgery centers participating in the North Italy Transplant program. Three hundred and nine patients (41%) had dilated, 9 (1%) restrictive, and 4 (0.5%) hypertrophic cardiomyopathy; 284 patients (38%) had ischemic, 65 (9%) valvular, and 22 (3%) congenital heart disease; 5 patients (0.5%) had primary pulmonary hypertension; 54 patients (7%) had other or nonspecified heart disease. Overall, 41 of 752 patients (5.4%) resulted anti-HCV–reactive. Serological evidence of HCV infection was found in 12 of 309 patients with DCM (3.9%; 95% CI, 1.7–6.0), and in 29 of 443 without DCM (6.5%; 95% CI, 4.2–8.8), without statistical difference (difference of prevalence rate: 2.6%; 95% CI, -4.9 to 5.8). In conclusion, HCV does not seem to have a primary role in the pathogenesis of DCM. However, since our findings are in disagreement with those obtained in smaller series of patients of other ethnicity, large studies from different countries should be conducted. ***J. Med. Virol. 58:116–120, 1999.***

KEY WORDS: HCV; antibodies; cardiac disease; heart transplantation

INTRODUCTION

Dilated cardiomyopathy (DCM) is a leading cause of heart failure and represents the principal indication for cardiac transplantation in both adults and children [Michels, 1993; Dec and Fuster 1994]. Previous studies indicated that infection with enterovirus, the most common agent causing human myocarditis, is associated with the development of the disease [Bowles et al., 1986; Muir et al., 1996; Baboonian and Treasure, 1997]. However, the enteroviral genome has been detected in the cardiac tissue samples from only a proportion of patients affected from DCM [Petitjean et al., 1992; Liljeqvist et al., 1993; Andreoletti et al., 1995; Muir et al., 1996; Baboonian and Treasure, 1997; Jeffery et al., 1997]. Hence, it is possible that other viral agents are related to the genesis of DCM.

Hepatitis C virus (HCV), a single-strand RNA virus belonging to the Flaviviridae family, is the principal causative agent of non-A, non-B hepatitis worldwide [Choo et al., 1989; Kuo et al., 1989; Alter et al., 1992;

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Tong et al., 1995; NIH Consensus Development Conference Panel Statement, 1997]. It is also involved in the pathogenesis of several extrahepatic diseases, such as essential mixed cryoglobulinemia [Agnello et al., 1992; Misiani et al., 1992], membranoproliferative glomerulonephritis [Johnson et al., 1993], and B-cell non-Hodgkin's lymphomas [Ferri et al., 1994; Silvestri et al., 1996; Zuckerman et al., 1997]. Recently, a high prevalence of HCV infection has been reported among patients with DCM [Matsumori et al., 1995; Matsumori and Sasayama, 1996]. In addition, HCV sequences have been detected in the myocardial tissue of patients with DCM [Matsumori et al., 1995] and in patients with chronic myocarditis [Okabe et al., 1997]. Taken together, these observations seem to indicate that HCV has a pathogenetic role in the development of DCM, and this could have important implications for the treatment of myocardial disease. However, studies on the association of HCV with DCM have been so far conducted in relatively small series of patients from Japan, and further information is therefore required.

This article presents the results of a multicenter study conducted among a cohort of 752 patients candidate to heart transplantation between 1995 and 1997 in the North Italy Transplant program (NITP), a transplant organization that includes six cardiac surgery centers. In the NITP area, HCV infection has a relatively high frequency among the population [Bellentani et al., 1994; Zanella et al., 1995; Prati et al., 1996, 1997, 1998a, 1998b] and ranks first as a cause of liver cirrhosis and hepatocellular carcinoma [Bellentani et al, 1994]. To establish whether HCV infection is associated with the development of DCM, the prevalence of antibodies to HCV was determined in patients with different diagnosis of end-stage heart disease.

MATERIALS AND METHODS

Patients

A total of 752 consecutive patients (608 males and 144 females; age, 53 ± 13 years) who entered the waiting list for cardiac transplantation from 1 June 1995 to 31 May 1997 at the six cardiac surgery centers participating in the NITP was enrolled. To be accepted on the waiting list, patients had to meet the following criteria: 65 years of age or younger; severe left ventricular dysfunction (echocardiographic left ventricular ejection fraction of 0.25 or less, increased to 0.35 in patients with significant mitral regurgitation); symptoms typical of New York Heart Association (NYHA) functional class III or IV; not affected by systemic diseases or other conditions contraindicating heart transplantation; and agreeing to signed informed consent.

For each patient, a serum sample and an informative record were sent to the NITP reference center in Milan. Information on the patients included demographic data, diagnosis, previous blood transfusion and thoracic surgical intervention, and results of laboratory tests, including alanine aminotransferase (ALT), hepatitis B surface antigen (HBsAg), and anti-HCV determination. Data from patients were entered into a database, and the serum samples were immediately stored at −40°C until use.

Of the 752 patients, 309 (41%) had dilated, 9 (1%) restrictive, and 4 (0.5%) hypertrophic cardiomyopathy; 284 patients (38%) had ischemic, 65 (9%) valvular, and 22 (3%) congenital heart disease; 5 patients (0.5%) had primary pulmonary hypertension; 54 patients (7%) had other or nonspecified heart disease.

Procedure

Alanine aminotransferase, HBsAg, and anti-HCV screenings were performed in the six participating centers using standard methods. The upper reference limit for ALT was 40 U/L. For anti-HCV screening, third-generation enzyme immunoassays (EIA) were used.

At the NITP reference center, samples showing anti-HCV reactivity by EIA were submitted to a serological confirmation using a third generation recombinant immunoblot assay (RIBA-3, Ortho Diagnostic Systems, Raritan, NJ). This test carries four different antigens in separate bands from structural and nonstructural regions of the virus. Samples were classified as positive when reactive to at least two bands, negative when not reactive, and indeterminate when a single-band reactivity was detected, as recommended by the manufacturer. On the basis of previous results [Zanella et al., 1995], patients were considered to have a true anti-HCV reactivity if found indeterminate or positive by RIBA.

Statistical Analysis

Prevalence rates were expressed as percent and 95% confidence intervals (CI). The calculation of the relative risk (RR) and 95% CI and the *t*-test were was used when appropriate. A P value of less than 0.05 by the *t*-test was considered statistically significant.

RESULTS

Fifty-four (7%) of the 752 patients were anti-HCV–positive by EIA screening. Of these, 41 (76%) were reactive (32 positive, 9 indeterminate) and 13 (24%) nonreactive by RIBA-3. Thus, the overall prevalence of confirmed anti-HCV reactivity was 5.4% (95% CI, 3.8–7.1). The main characteristics of anti-HCV–positive patients are shown in Table I. Anti-HCV–positive patients had a higher frequency of previous thoracic surgery than those anti-HCV–negative. The age and ALT distribution between the two groups were not statistically different.

The demographic and clinical characteristics of the study population according to the diagnosis of heart disease are reported in Table II. A higher frequency of previous blood transfusion and thoracic surgical intervention was observed in patients with ischemic, valvular, and congenital heart disease, as compared to patients with other causes of heart failure. In addition, patients with valvular disease showed an increased risk of anti-HCV reactivity. Serological evidence of HCV infection was found in 12 of 309 patients with DCM (3.9%; 95% CI, 1.7–6.0) and in 29 of 443 without

TABLE I. Parenteral Risk Factors, HBsAg Reactivity, and ALT Levels in 752 Patients With End-Stage Heart Disease, Grouped According to the Results of Anti-HCV Determination[a]

	Gender M/F	Age (years) mean ± SD	Number (%) with previous blood transfusion	Number (%) with previous thoracic surgery	Number (%) HBsAg-positive	ALT levels mean ± SD
Anti-HCV–reactive (n = 41)	28/13	57 ± 10	12 (29%)	8 (20%) RR, 2.8 95% CI, 1.4–5.5	2 (5%)	37 ± 43
Anti-HCV–negative (n = 711)	580/131	53 ± 14	143 (20%)	50 (7%)	26 (4%)	32 ± 35

[a]The relative risk (RR) and the 95% confidence interval (95% CI) are indicated in case of a significant association.

TABLE II. Demographic and Clinical Characteristics of the Study Patients, Grouped According to the Diagnosis of Heart Disease[a]

Diagnosis	Number of subjects	Gender M/F	Age (years) mean ± SD	Number (%) with previous blood transfusion	Number (%) with previous thoracic surgery	Number (%) with confirmed anti-HCV reactivity	Number (%) HBsAg-positive
Dilated cardiomyopathy	309	238/71	53 ± 13	19 (6.1%) RR, 0.2 95% CI, 0.1–0.3	3 (0.9%) RR, 0.07 95% CI, 0.03–0.2	12 (3.9%)	12 (3.9%)
Restrictive cardiomyopathy	9	6/3	46 ± 13	1 (11.1%)	0	0	0
Hypertrophic cardiomyopathy	4	0/4	46 ± 28	0	1 (25%)	0	0
Ischemic heart disease	284	266/18	59 ± 8	85 (29.9%) RR, 2.0 95% CI, 1.5–2.6	30 (10.6%) RR, 1.8 95% CI, 1.1–2.1	14 (4.9%)	9 (3.1%)
Valvular heart disease	65	49/16	56 ± 8	36 (55.4%) RR, 3.2 95% CI, 2.4–4.2	18 (27.7%) RR, 4.76 95% CI, 2.9–7.0	12 (18.5%) RR, 4.4 95% CI, 2.3–8.1	2 (3.1%)
Congenital heart disease	22	14/18	27 ± 11	10 (45.4%) RR, 2.3 95% CI, 1.4–3.7	5 (22.7%) RR, 3.1 95% CI, 1.4–7.0	2 (9%)	0
Primary pulmonary hypertension	5	2/3	37 ± 10	0	0	0	0
Other heart disease/ unknown	54	33/21	36 ± 18	4 (7.4%)	1 (1.8%)	1 (1.8%)	5 (9.2%)
Overall	752	608/144	53 ± 13	155 (20.6%)	58 (7.7%)	41 (5.4%)	28 (3.7%)

[a]The relative risk (RR) and the 95% confidence interval (95% CI) are indicated in case of a significant association.

DCM (6.5%; 95% CI, 4.2–8.8), without statistical difference (difference of prevalence rate: 2.6%; 95% CI, –4.9 to 5.8).

DISCUSSION

The hepatitis C virus is an important cause of both acute and chronic liver disease [Choo et al., 1989; Kuo et al., 1989; Alter et al., 1992; Tong et al., 1995; NIH Consensus Development Conference Panel Statement, 1997]. In addition, the clinical spectrum of HCV infection includes several nonhepatic diseases and manifestations [Agnello et al., 1992; Misiani et al., 1992; Johnson et al., 1993; Ferri et al., 1994; Silvestri et al, 1996; Zuckerman et al., 1997]. Recent epidemiological and histological studies from Japan suggested that HCV has a role in the development of DCM [Matsumori et al., 1995; Matsumori and Sasayama, 1996; Okabe et al., 1997]. Our analysis was conducted to test this hypothesis in a large cohort of Italian patients with end-stage heart failure. The results could be useful to decide on the opportunity of implementing experimental trials for the antiviral treatment of HCV-associated myocardial disease, as already suggested [Matsumori et al., 1995; Matsumori and Sasayama, 1996].

The overall prevalence of anti-HCV reactivity in this study was 5.4%, a figure higher than that previously observed among blood donors (1.1%) [Prati et al., 1996], and comparable to that reported in the general population of Northern Italy (3.2%) [Bellentani et al., 1994]. Moreover, the seroprevalence of anti-HCV was slightly higher than that of HBsAg, in agreement with previous reports indicating that HCV is responsible for the majority of chronic hepatotropic infections in our area [Bellentani et al., 1994].

The frequency of anti-HCV in patients with end-stage DCM (3.9%) did not differ from that observed among patients with other causes of heart failure (6.5%). Thus, the findings do not confirm the prelimi-

nary data obtained by Matsumori et al. [1995] and Matsumori and Sasayama [1996], who found a higher prevalence of anti-HCV reactivity among DCM patients as compared to controls (16.7% vs. 2.5%), and hypothesized the existence of a pathogenetic link between HCV infection and genesis of DCM. This discrepancy may be due to a number of reasons.

A first hypothesis is that some of the factors that can be determinant in inducing HCV-associated cardiomyopathy (for example, immunologic or genetic features of the host and/or specific viral strains) are differently expressed in the two populations. Indeed, there is substantial evidence that both host and viral factors can influence the natural course of HCV infection and the response to antiviral therapy [Prati et al., 1996; Alric et al., 1997; Herion and Hoofnagle, 1997]. Moreover, significant differences between Japanese and Western clinical therapeutic trials have been reported, which could be attributed to HCV heterogeneity [Herion and Hoofnagle, 1997]. On the other hand, the observation that the clinical manifestations unequivocally associated with HCV infection (i.e., chronic hepatitis, hepatocellular carcinoma, mixed cryoglobulinemia, and B-cell non-Hodgkin's lymphomas) are limited neither to a particular geographic area nor to viral types renders this hypothesis not completely convincing.

Alternatively, the possibility of a referral bias affecting our conclusions should be considered, since we limited our analysis to patients with end-stage heart failure, and we excluded those affected by symptomatic liver disease (i.e., those with sign or symptoms of decompensated liver cirrhosis or affected by hepatocellular carcinoma). In this regard, the existence of particular cases of HCV-induced DCM characterized by mild cardiac symptoms and/or by clinically advanced hepatic disease is theoretically possible. Nevertheless, in the Japanese series [Matsumori et al., 1995; Matsumori and Sasayama, 1996; Okabe et al., 1997], patients with HCV infection had a severe outcome of cardiac disease, in agreement with the previous finding that advanced heart failure is the first manifestation of DCM in the vast majority of the cases [Sugrue et al., 1992]; in addition, liver disease was absent or well compensated. On the basis of these considerations, we believe that the referral bias does not offer a reasonable explanation for the discrepancy with the previous reports.

Finally, the disagreement may simply reflect the methodological differences (i.e., size of the study population, study design) between the prior investigations and the present one. In fact, the study by Matsumori et al. [1995] was conducted on a relatively small series of cardiac patients (36 with DCM and 40 without DCM) recruited in a single center. Interestingly, the same group recently reported a high frequency of HCV infection (10.6%–17.1%) also in patients with hypertrophic cardiomyopathy [Matsumori et al., 1996, 1998], a disease that does not seem to be caused by viral infection [St. John Sutton and Epstein, 1998].

In the absence of a clear-cut epidemiological association between HCV infection and DCM, the previous finding reported by Matsumori et al. [1995] and Okabe et al. [1997] that negative-strands of HCV RNA can be detected in the myocardium of patients with DCM or myocarditis should not be interpreted as an independent proof for the pathogenetic relationship between HCV infection and cardiac disease. Indeed, recent studies performed with highly strand-specific RT-PCR suggest extreme caution in interpreting experiments in which detection of HCV RNA strand polarity was claimed [Lanford et al., 1995]. Moreover, the possibility of myocardial contamination with HCV RNA from HCV-infected peripheral leukocytes can not be excluded [Matsumori et al., 1995].

Unexpectedly, it was found that patients with valvular heart disease had a higher frequency of HCV infection than those with other causes of cardiac failure. However, they also had a more frequent exposure to parenteral risk factors, such as blood transfusion and thoracic surgery, as a consequence of their disease. Hence, this association is probably the result of differences in the clinical management of the patients and does not indicate a role for HCV in the pathogenesis of valve dysfunction.

In conclusion, HCV does not seem to have a primary role in the pathogenesis of DCM. Therefore, the implementation of clinical trials for the antiviral treatment of DCM patients who have HCV infection, which have been suggested by some authors, is not advisable at the present time. However, since our findings are in disagreement with those obtained in smaller series of patients of other ethnicity, large studies from different countries are necessary to collect conclusive evidence on this issue. Complementary studies, looking for evidence of DCM in patients with known HCV infection, might also be opportune.

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